

N-Substituted Lactamides

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RECEIVED JANUARY 2, 1953

N,N-Disubstituted lactamides that are difficult to obtain by aminolysis of methyl lactate with secondary amines were readily prepared by dehydration of the lactic acid-secondary amine salt. The preparation and properties of various dialkyl, alkyl aryl, aralkyl and hydroxyalkyl lactamides are reported.

Previous papers from this Laboratory reported that N-monosubstituted lactamides can be prepared in excellent yields by aminolysis of methyl lactate with primary aliphatic amines.^{2,3} The reaction is simple, proceeds readily at room temperature, and in most instances results in almost quantitative yields of the substituted lactamide. With a few exceptions, the N,N-disubstituted lactamides, however, were extremely difficult to prepare by such an aminolysis reaction. The notable exceptions were aminolysis of methyl lactate with dimethylamine, piperidine, morpholine, pyrrolidine and diethanolamine, in which instances the yields of N,N-disubstituted lactamide were extremely

high.^{4,5,6} Thus, N,N-dimethyl lactamide was obtained in 90% yield, whereas N,N-dibutyl lactamide was virtually unobtainable by aminolysis of methyl lactate with the appropriate secondary amine.

In the study reported here, the preparation of dialkyl lactamides by dehydration of the lactic acid-secondary amine salt was investigated. This general method for the preparation of amides has been applied previously in making aromatic derivatives such as lactanilide.^{7,8} N,N-Dibutyl lactamide has been suggested as a plasticizer for

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) W. P. Ratchford, *J. Org. Chem.*, **15**, 326 (1950).

(3) W. P. Ratchford and C. H. Fisher, *ibid.*, **15**, 317 (1950).

(4) W. P. Ratchford and C. H. Fisher, *THIS JOURNAL*, **69**, 1911 (1947).

(5) W. P. Ratchford, J. H. Lengel and C. H. Fisher, *ibid.*, **71**, 647 (1949).

(6) W. P. Ratchford, *Ind. Eng. Chem.*, **42**, 1565 (1950).

(7) Leipen, *Monatsh.*, **9**, 45 (1888).

(8) C. A. Bischoff and P. Walden, *Ann.*, **279**, 71 (1894).

TABLE I
PREPARATION AND PROPERTIES OF N-SUBSTITUTED LACTAMIDES

Lactamide	Reaction conditions ^a		Conver- sion, %	Physical constants and analysis ^b			Nitrogen, %				
	Temp., °C.	Time, hr.		°C.	B.p., Mm.	M.p., ^c °C.	<i>n</i> _D ²⁰	<i>d</i> ₄ ²⁰	η at 20° c.p.s.	Found	Calcd
N,N-Diallyl	141-160	8	68	111	5.0		1.4792	1.0115	14.38	8.01	8.28
N,N-Di- <i>n</i> -butyl	165-187	7	83	145	10.0		1.4540	0.9413	22.05	6.81	6.96
N,N-Di- <i>n</i> -amyl	151-158	8	80	150	5.0		1.4552	.9227	27.27	6.09	6.11
N,N-Di- <i>n</i> -hexyl	147-161	8	81	154	2.0		1.4566	.9158	34.89	5.32	5.44
N,N-Di- <i>n</i> -octyl ^h	170-183	5	77 ^d	204	4.0		1.4590	.9018	45.89	4.34	4.47
N,N-Di-2-ethylhexyl ⁱ	162-184	5	60 ^d	179	4.0		1.4612	.9108	94.85	4.33	4.47
N,N-Di- <i>n</i> -decyl ^j	149-156	8	83	145	0.004		1.4605	.8892	55.71	3.68	3.79
N,N-Dibenzyl	176-182	6	75	134	.015	73-74	1.5700 ^e			5.22	5.20
N-Butyl-N-phenyl	159-172	7	28 ^d	134	1.7	38.5-39.5	1.5159 ^e			6.21	6.33
N-Methyl-N-phenyl	153-164	11	50 ^d			89-90				7.75	7.82
N-Phenyl ^f	110-134	5	87	149	0.9	57-58	1.5635 ^e				
N- <i>t</i> -Octyl	136-146	9	44	80	.01		1.4585	.9530	202.4	6.78	6.96
N-(α -Methylbenzyl) ^g			50	102	.001	92-94	1.5338 ^e			7.28	7.25
N-(β -Phenylethyl) ^g			95			86-87				7.28	7.25
N-(3-Hydroxypropyl) ^g			91	116	.001		1.4848	1.1507		9.64	9.52
N-(1-Hydroxy-2-butyl) ^g			88	111	.02		1.4781	1.1052		8.56	8.69
N,N-Dibutylpropionamide	163-181	11	53	122	10.0		1.4469	0.8758	4.43	7.42	7.56

^a Reaction temperature and time were recorded after free water from the 80% lactic acid had been removed. ^b Determined on redistilled or recrystallized materials. ^c N-Methyl-N-phenyllactamide was recrystallized from acetone, the others from ether. ^d Unreacted amine was also recovered in appreciable quantity (10 to 60%). ^e Supercooled liquid. ^f Previously reported (ref. 7 and 8). ^g Prepared by aminolysis of methyl lactate with the appropriate amine. ^h Calcd. for C₁₉H₃₉O₂N: C, 72.79; H, 12.54. Found: C, 72.70; H, 12.55. ⁱ Calcd. for C₁₉H₃₉O₂N: C, 72.79; H, 12.54. Found: C, 72.69; H, 12.52. ^j Calcd. for C₂₃H₄₇O₂N: C, 74.74; H, 12.82. Found: C, 74.71; H, 12.96.

zein,⁹ but its preparation and physical properties were not described. Dehydration of the lactic acid-secondary amine salt proved to be a highly satisfactory method for preparing the disubstituted lactamides. The procedure was simple; it consisted in neutralizing aqueous lactic acid with the amine, then dehydrating by refluxing with a high-boiling entraining agent such as xylene.

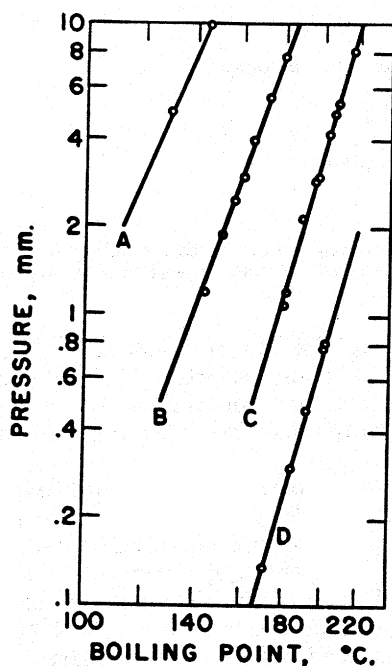


Fig. 1.—N-Disubstituted lactamides: A, di-*n*-butyllactamide; B, di-*n*-hexyllactamide; C, di-*n*-octyllactamide; D, di-*n*-decyllactamide.

(9) C. D. Evans and R. H. Manley, U. S. Patent 2,437,946, March 16, 1948.

Water present as solvent was removed rapidly, whereas dehydration of the salt to amide occurred more slowly and at temperatures in the neighborhood of 150°. In general, conversion into the amide was in the range of 70 to 85%. Secondary amines containing one aryl substituent on the nitrogen and primary aliphatic amines derived from a tertiary alkyl group, such as *t*-octylamine, were not so satisfactory as the simpler secondary amines in this reaction, and were also non-reactive in the aminolysis of methyl lactate. The lactamides were high-boiling materials; those containing an aromatic ring were solids at room temperature. In the preparation of N-methyl-N-phenyl- and N-butyl-N-phenyllactamides large amounts of unreacted amine were recovered and a considerable quantity of lactide was formed.

Experimental

Amines.—Commercial materials were redistilled; they had the following constants: Diallylamine, b.p. 110° at about 760 mm., n_D^{20} 1.4402; di-*n*-butylamine, b.p. 158.5° at about 760 mm., n_D^{20} 1.4182; di-*n*-amylamine, b.p. 77.5° at 9 mm., n_D^{20} 1.4270; di-*n*-hexylamine, b.p. 104° at 7 mm., n_D^{20} 1.4338; di-(2-ethylhexyl)-amine, b.p. 126° at 4.0 mm., n_D^{20} 1.4431; di-*n*-octylamine, b.p. 151° at 5.0 mm., n_D^{20} 1.4345; didecylamine, b.p. 184-186° at 3.0 mm.; dibenzylamine, b.p. 151.5-152° at 5.0 mm., n_D^{20} 1.5760; aniline, b.p. 75-76° at 15 mm.; N-methylaniline, b.p. 79.5-81° at 12 mm., n_D^{20} 1.5697; and N-butylaniline, b.p. 111-112° at 10 mm., n_D^{20} 1.5339.

Lactamides Obtained by Dehydration of Lactic Acid-amine Salts.—The following procedure for the preparation of N,N-dibutylactamide was typical of the preparation of the various lactamides.

Edible grade 80% lactic acid (112 g., 1 mole of total available lactic acid) was neutralized with the equivalent amount of dibutylamine (129 g., 1.0 mole) which was added portionwise and with occasional cooling and shaking. Then xylene (100 ml.) was added, and the two-phase reaction mixture, continuously stirred, was refluxed under a water-separating trap, commonly used for removing water formed in esterification reactions. Thus water was continuously removed by xylene, the entraining agent. The water normally

present in the 80% lactic acid (*ca.* 22 ml.) was removed rapidly, but the water resulting from dehydration of the amine lactate was formed at higher temperature and at a considerably slower rate. After removal of free water, 11 hours of refluxing at 154 to 166° was required to collect 18 ml. (1 mole) of water formed by dehydration of the salt. By using less entraining agent (50 ml. instead of 100 ml.) the reaction temperature was increased, and dehydration was completed considerably faster (7 hours instead of 11).

Upon completion of the reaction, the xylene was removed by distillation at 40–50 mm., and the dibutylactamide was isolated by distillation at 5.0 mm.

The preparation of other substituted lactamides is summarized in Table I. The physical constants and analytical data were determined on redistilled or recrystallized samples. The solid lactamide derivatives were recrystallized from ether, except N- β -phenylethylactamide, which was recrystallized from acetone. For purposes of comparison, N,N-dibutylpropionamide was also prepared.

Lactamides by Aminolysis of Methyl Lactate.—N-(α -methylbenzyl)-, N-(β -phenylethyl)-, N-3-hydroxypropyl- and N-(1-hydroxy-2-butyl)-lactamides were prepared by aminolysis of methyl lactate with an equivalent amount of α -methylbenzylamine, β -phenylethylamine, 3-aminopropanol and 2-amino-1-butanol, respectively. This method has been described previously.^{3,6} The results are shown in Table I.

Boiling points of dibutyl, dihexyl, dioctyl and didecyl lactamides were determined at various pressures in the range

of 0.1 to 10.0 mm. with a tensimeter still.¹⁰ The results are shown in Fig. 1.

Acknowledgment.—The authors wish to thank Mary Jane Welsh and Ruth Kelly of this Laboratory for the analyses and T. J. Fitzpatrick for help in several preparations. They also thank the following companies¹¹ for generous samples: Sharples Chemical, Inc., for dibutylamine, diamylamine, dihexylamine, didecylamine, N-butylaniline; Heyden Chemical Company for dibenzylamine; Carbide and Carbon Chemicals Corp. for di-2-ethylhexylamine, N- α -methylbenzylamine; Rohm and Haas Co. for *t*-octylamine; Monsanto Chemical Co. for β -phenylethylamine; Shell Development Co. for diallylamine; Commercial Solvents Company for 2-amino-1-butanol; American Cyanamid Co. for 3-aminopropanol.

(10) W. P. Ratchford and C. E. Rehberg, *Anal. Chem.*, **21**, 1417 (1949).

(11) Mention of names, brands or companies should not be construed as a recommendation or endorsement by the Department of Agriculture over those not mentioned.

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